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In re the Application of ) Group Art Unit: 1632  
James M. Wilson et al )  
Appln No. 09/242,977 ) Examiner: J. Martin  
Filed: February 26, 1999 )  
For: METHOD FOR RECOMBINANT )  
ADENO-ASSOCIATED VIRUS- )  
DIRECTED GENE THERAPY )

Asst. Commissioner for Patents  
Washington, DC 20231

**DECLARATION PURSUANT TO 37 CFR §1.131**

I, James M. Wilson, residing at 1350 N. Avignon Drive, Gladwyne, Pennsylvania 19034, do declare and state that:

1. I am a named co-inventor of the subject matter claimed in the above-identified application.
2. I understand that this Declaration is being submitted to establish a date of invention in the United States prior to July 26, 1996, which is the date on which the publisher has indicated that Gouras et al, Neurobiology of Aging, 1996 was released.

**CERTIFICATE UNDER 37 CFR 1.8(a)**

I hereby certify that this correspondence is being deposited with the United States Postal Service, postage pre-paid, as first class mail on the date indicated below in an envelope addressed to: Asst. Commissioner for Patents, Washington, DC 20231

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3. Attached is a Preliminary Invention Disclosure Form, dated prior to July 26, 1996, which demonstrates conception of the invention in the United States. The dates from this Disclosure Form, as well as the portions which are not relevant to the claimed subject matter, have been redacted.

4. In Paragraph 4, the Preliminary Invention Disclosure Form provides evidence of conception and actual reduction of an rAAV comprising ApoE according to the invention. In addition, a clinical model for testing muscle-directed gene transfer with a composition containing the recombinant AAV that expresses ApoE is described. The acts described in this Form were performed by me, or under my direct supervision.

5. Work continued on the claimed subject matter, both by me and under my supervision in the United States. This work involved our assistance in preparation of the priority patent applications and further scientific studies, including use of the compositions of the invention in animal experiments. This work continued until the filing date of US Patent Application No. 09/708,188, filed September 6, 1996, and further continued until at least the filing dates of continuation-in-part application No. 09/729,061, filed October 10, 1996, and international patent application PCT/US97/15691, filed September 4, 1997.

6. The facts provided in Paragraph 3-5 and attached Exhibit A demonstrate conception and actual reduction to practice prior to July 26, 1996 for at least some of the claimed subject matter. These facts further demonstrate conception of the invention prior to July 26, 1996, followed by diligence and constructive reduction to practice, which is evidenced by the filing of the priority applications. The facts provided herein demonstrate invention of the claimed subject matter in the United States prior to July 26, 1996.

7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are

believed to be true; and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date 12-19-00

By James M. Wilson

James M. Wilson, M.D., Ph.D.

## DISCLOSURE STATEMENT

University of Pennsylvania:GENOVO Sponsored Research

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**Relevant Patents:**

[illegible]

Not relevant ☐

Notes: The use of recombinant adeno-associated viruses for muscle directed gene therapy. [REDACTED]  
To be considered for filing a new patent.

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# Exhibit A

University of Pennsylvania  
Preliminary Invention Disclosure Form

Working title: The use of recombinant adeno-associated viruses (AAV) for muscle directed gene therapy

Description of technology:

Adenoassociated viruses (AAV) have been considered as vectors for gene therapy. We recently discovered that much of the literature on recombinant AAV was confounded by the fact that preps of the virus were contaminated with adenovirus. Upon complete purification of recombinant AAV, we found that it no longer effectively transduced cells in culture, or epithelial cells in lung and liver *in vivo*. Apparently, the helper adenovirus expresses genes in trans which facilitate the conversion of single-stranded AAV genome to a double-stranded, non-integrated form which is receptive to RNA polymerase II leading to transcription of RNA and, eventually, expression of the gene. Please note that our description of transduction here is expression of a recombinant gene; this does not imply that the recombinant gene is integrated. The bottom line of our initial work is that purified AAV used for *in vitro* studies, as well as in liver and lung *in vivo*, was not efficient in the context of recombinant gene transduction.

We found, somewhat serendipitously, that direct injection of purified recombinant AAV into skeletal muscle did lead to very efficient gene transduction that was perfectly stable. Our work in follow-up has proceeded along in several paths.

1. Mechanism of stable transduction. We have demonstrated that recombinant AAV in muscle very efficiently transfers its genome into non-dividing skeletal myotubes and integrates its genome into the chromosomal DNA. Expression is perfectly stable for well over six months without apparent diminution and is widely efficient when infiltrated into skeletal muscle.
2. We have learned that expression of genes encoding foreign proteins from recombinant AAV remarkably is associated with little destructive cellular or humoral immune responses. This is in contrast to adenovirus which augments and stimulates the development of destructive immune responses to the transgene product when this product is viewed by the recipient as a neoantigen. We have now defined the mechanisms responsible for the destructive immune responses in adenoviruses that are not present in AAV.
3. The studies described above were developed in the context of various murine models. Similar results have recently been obtained in nonhuman primate skeletal muscle.
4. We have now established three relevant clinical models to test the concept of muscle directed gene transfer with recombinant AAV.

[REDACTED]

[REDACTED] In addition, we have recently developed a recombinant AAV that expresses ApoE, an important constituent of LDL. When this apoprotein is low or absent, patients develop hypercholesterolemia. This will be studied in the context of an ApoE deficient mouse. [REDACTED]

[REDACTED]

Those (other than listed inventors) who worked on the technology:

[REDACTED]

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